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Sodium-directed selective cleavage of lactones: a method for structure determination of cyclodepsipeptides

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Abstract

A strategy is presented for the determination of amino-acid sequences of cyclodepsipeptide antibiotics. A highly specific sodium-ion interaction with the backbone lactone opens the depsipeptide ring to form a linear acylium ion or isomeric equivalent. When activated by high energy collisions on a tandem mass spectrometer or by low energy collisions on an ion trap, the acylium ion undergoes sequence-specific fragmentation to yield a simple product-ion mass spectrum. Fragmentation is charge-driven, and amino acid residues are sequentially deleted from the C-terminus of the acylium ion. Interferences from indiscriminate ring opening at backbone amide bonds are eliminated. The method is suited to the structural analyses of various cyclodepsipeptides, including those with linear peptide moieties. Results are presented for beauvericin, didemnin B, and enniatin B1, representing the three commonly encountered structural variations in cyclodepsipeptide antibiotics. (Int J Mass Spectrom 182/183 (1999) 289–298) © 1999 Elsevier Science B.V.

Keywords: Cyclodepsipeptides; Specific sodium-ion interaction; Peptide sequencing, Ion-trap MS; Four-sector MS

1. Introduction

Cyclodepsipeptides (peptide lactones) are a diverse class of natural products that possess at least one ester linkage in their backbones. Many cyclodepsipeptides are ionophore antibiotics, which means that their antimicrobial activities are related to a highly selective interaction with sodium or potassium ions. Valinomycin, for example, binds potassium ions one thousand times more strongly than it binds sodium ions [1].

Mass spectrometric determination of the amino-acid sequences of cyclodepsipeptides is complicated by interferences from indiscriminate and multiple-ring opening pathways (for a review, see [2]). One strategy adopted by Das and co-workers [3] to solve this problem was to form the ions by chemical ionization and utilize a preferential ring opening at the depsipeptide ester bond to assign amino-acid sequences. The authors proposed that protonation of an ester oxygen opened the ring to form a linear peptide with a C-terminal carboxylic acid that fragmented to furnish the amino-acid sequence. They, however, pointed out that ring opening probably occurred less specifically when the molecule contained more than

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Dedicated to the memory of Professor Ben S. Freiser.

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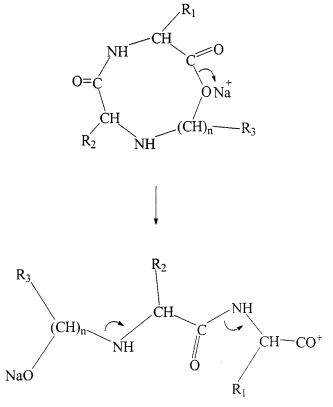
one ester linkage. Preferential ring opening at an ester linkage was also proposed by Roboz and co-workers [4]. On the contrary, Lange and co-workers [5–7], in their tandem mass-spectrometry study of the cyclodepsipeptides destruxins, which were introduced into the instrument by fast atom bombardment (FAB), and Suzuki et al., and Myokei et al. [8,9] observed that ring opening occurred at the amide bonds rather than at ester linkages. These contradictions are illustrative of the complexity endemic in deriving sequence information from the product-ion mass spectra of cyclodepsipeptides.

Another approach that utilizes chemical pretreatment is by Zink and co-workers [10], who utilized mild methanolysis in HCl to convert conchinmycins into linear methyl-ester derivatives. Subsequent tandem mass spectra of the linear methyl esters afforded useful sequence information. In a related approach, Sugawara et al. [11] hydrolyzed the lactone linkage in empedopeptin under basic conditions to form empedopeptinic acid and determined the product by mass spectrometry. Bateman et al. [12] used an enzyme-catalyzed hydrolysis of the lactone bonds in etamycin and streptogramin B antibiotics followed by liquid chromatography/mass spectrometry (LC/MS) and LC/MS/MS to sequence the ring-opened depsipeptides. In all of these studies, hydrolysis was a first step and assignments of amino-acid sequences of the hydrolysates were feasible because the antibiotics contained only one ester linkage.

We describe here a completely instrumental strategy in which the $[M + Na]^+$ ion is submitted to collisional activation. The underlying hypothesis is that the oxyphilic Na^+ would interact with the ester oxygen to open the depsipeptide ring (Scheme 1). Upon collisional activation, the ring-opened structure would presumably undergo a charge-driven, sequence-specific fragmentation to yield a simple mass spectrum. We present results for the interactions of Na^+ with beauvericin, didemnin B, and enniatin B1, representing the three commonly encountered structural variations in cyclodepsipeptide antibiotics.



Scheme 1.

Beauvericin is a typical symmetrical cyclodepsipeptide. It has equal numbers of ester and amide linkages in the backbone and acts as an ionophore antibiotic. Beauvericin is isolated from the fungal strains of Fusarium spp FO-740 and FO-1305, and from the mycelia *Beauveria bassiana* [13,14]. It is a very potent toxin to brine shrimps and mosquito larvae, and was recently recognized as one of the most potent and specific acyl-CoA:cholesterol acyl transferase (ACAT) inhibitors [15,16].

Didemnin B [17–26] is an irregular cyclodepsipeptide, which also has a linear peptide chain attached to the cyclodepsipeptide backbone. The didemnins are isolated from tunicates of the family Didemnidae: *Tridemnum solidum* and *Tridemnum cyanophorum*. All didemnins contain the same macrocycle core structure and differ only in the side chains attached to the backbone through the amino group of threonine. Didemnin B exhibits high cytotoxicity, specific antiviral and immunosupressant activities, and has potential as an anticancer and antivirus drug [16–18].

Enniatin B [16] contains equal numbers of amide and ester bonds in its backbone, but has an unsymmetrical distribution of side chains. It is a member of the enniatin family of ionophore antibiotics. At least eight enniatins, A, A1, B, B1, C, D, and F, were isolated from fungal strains and characterized [16]. Enniatin B1 is also a potent inhibitor of acyl-CoA: cholesterol acyl transferase (ACAT) [16].

We are pleased to dedicate this article to the memory of Professor Ben Freiser. Because the subject of metal-ion interactions with organic molecules was the theme of his research career, we hope this article is an appropriate dedication.

2. Experimental

Beauvericin and a crude mixture of enniatins were purchased from Sigma Chemical Co (St. Louis, MO). Didemnin B was provided by the Drug Synthesis and Chemistry Branch of the National Cancer Institute.

2.1. FAB and high-energy CAD

Fast-atom bombardment (FAB) and high-energy collision-activated dissociation (CAD) mass spectra of didemnin B were acquired on a VG ZAB-T high performance four-sector mass spectrometer (VG Analytical, Manchester, UK). An aliquot of 0.5 μL of 3-nitrobenzyl alcohol (Aldrich Chemical Co, Milwaukee, WI) was placed on a FAB probe tip, and approximately 0.5 μL of a 2 nmol/μL didemnin B solution in water was placed on the matrix drop on the FAB probe tip. The sample was bombarded with a 25-keV cesium beam. The resulting gas-phase $[M + H]^+$ ions were accelerated to 8 keV and selected by MS1, which had been set at a static resolving power of 1500 (full width at half maximum or FWHM). The collision cell was floated at 4 kV, with the result that the ions had 4 keV of kinetic energy in the laboratory frame upon impact with the target helium gas in the collision cell. Helium gas was introduced into the collision cell at a pressure sufficient to attenuate the precursor-ion intensity by approximately 50%. The resulting product ions were analyzed by MS2 at a resolving power of 1000 (FWHM). For the determination of the $[M + Na]^+$, the experimental procedure was the same as above, except that the 3-nitrobenzyl-alcohol matrix was saturated with sodium iodide. Data acquisition and analyses were carried out with a VG (VG Analytical, Manchester, UK) data system equipped with a DEC Alpha 3000 workstation, OPUS V 3.1X software, and a VG SIOS I interface.

2.2. Ion-trap mass spectrometry

Low-energy, collisionally activated decomposition (LE CAD) experiments were carried out with a Finnigan LCQ (Finnigan MAT, San Jose, CA) ion-trap mass spectrometer equipped with the commercial Finnigan capillary electrospray-ionization source. The spray needle was at a potential of 5.5 kV, and a 4800 kPa coaxial flow of nitrogen was used to stabilize the spray. The counter electrode was a heated (199 °C) stainless-steel capillary held at a potential of 10 V. Tube-lens offset was 65 V, and electron multiplier voltage was 784.44 V. Helium gas was introduced into the center of the ion trap at a pressure of 1 mTorr to improve the trapping efficiency of the sample ions introduced into the ion trap. The background helium gas also served as the collision gas during the CAD event.

A 300–500 fmol/μL aqueous solution of the cyclic peptide solution in 20:80 MeOH:H_2O was infused into the mass spectrometer via a 250-μL Hamilton syringe (Hamilton Co., Reno, NV) at a flow rate of 2 μL/min. Mass spectra were acquired in the full scan and profile modes. No sodium was added to the instrument or sample solutions as there was sufficient background sodium in the sample tubing to provide for cationization.

The sodium adducts were selected and subjected to CAD. In the course of the experiments, it was determined that retention of about 10% to 20% of the precursor ions in the product-ion spectra would provide approximate optimum setting of the percentage relative collision energy for CAD experiments. Effective isolation-width settings for MS^2 experiments ranged from 0.7 to approximately 2 Da. To carry out MS^3 experiments on low-abundance ions formed in a first stage of collisional activation, the isolation width at the MS^2 stage was opened so that a sufficient number of ions would be available for a second stage of activation; emphasis at this stage was not on precise selection of the precursor. However, it was imperative that the isolation width be set at 1 Da or less at the MS^3 stage, otherwise the spectrum might be contaminated with spurious ions, and the residual precursor ion might assume a jagged peak profile. The number of microscans used in MS^2 experiments ranged from 10 to 20, depending on the intensities of the fragment-ion signals. Because some of the ions activated in the MS^3 experiments had low abundancies, a much larger number of microscans, up to 60,

Table 1
Some instrumental settings for the multistep CAD of the $[M + Na]^+$ of Didemnin B and Enniatin B1

MS^n	Precursor ion (m/z)	Isolation width (Da)	Relative collision energy (%)	# scans	# of μscans
Didemnin B					
2	1134	1	35	25	40
3	943	6, 1	35, 29	25	60
4	846	5, 5, 2	35, 29, 27	12	60
5	577	10, 10, 1	34, 32, 30, 22	27	40
6	420	10, 10, 10, 1.5	34, 32, 30, 22, 17	101	60
Enniatin B1					
2	676	1	35	25	10
3	563	4, 1	29, 20.6	6	10
4	463	4, 4, 1	29, 20.6, 16	5	20
5	350	5, 5, 5, 2	29, 20.6, 16, 15	12	20
Enniatin B1					
2	676	1	35	25	10
3	549	5, 1	29, 20	25	20
4	449	5, 5, 2	35, 29, 27	12	20
5	336	10, 10, 10, 1.5	29, 20.6, 16, 14.5	14	20

were used. Table 1 gives some of the instrumental settings for the multistep CAD experiments.

2.3. Nomenclature

Fragment ions are labeled according a nomenclature system developed by us [27]. The system makes use of the general formula x_{nJZ} where "*x*" is the designation for the ion (lower case "*a*," "*b*," "*c*"). Thus, a "*b*" ion is the traditional acylium ion, which may lose carbon monoxide to form an "*a*" ion, and "*n*" is the number of amino-acid residues in the ion. "J" and "Z" are the one-letter codes for the two amino-acid residues connecting the backbone amide or ester bond, J–Z, that was broken to form the decomposing linear ion. "J" is the N-terminal amino-acid residue and "Z" is the C-terminal amino-acid residue. When a fragment ion is sodiated, sodium is omitted from the label for simplicity, and the fragment is designated by a superscript *, where, for example, $b^*_{nJZ} = [b_{nJZ} - H + Na]$. Although the nomenclature is derived on the assumption of a reaction mechanism for fragmentation, the purpose is to designate product ions not to specify their origins.

3. Results and discussion

3.1. Beauvericin

The effect of sodium-ion attachment becomes most evident upon comparison of the product-ion spectrum of $[M + Na]^+$ ions with that of $[M + H]^+$ ions. The ion-trap CAD spectrum of protonated beauvericin [Fig. 1(A)] produced by electrospray ionization (ESI) is a superposition spectrum, consisting of overlapping patterns of all fragments arising from scission of all the ester and amide bonds of the molecule (Table 2). It is difficult to derive the amino-acid sequence from such a spectrum, even with the relatively abundant *c* ions that arise from ring scission at ester bonds. For example, c_2, c_3, and c_4 ions are observed, but the c_5 ion at m/z 702 is clearly missing from the spectrum even though beauvericin is comprised of a six amino-acid ring.

There are interesting features of the ion-trap CAD spectrum of the sodiated molecule [Fig. 1(B)]. First, the amino-acid sequence is furnished by a simple set of *b** ions: $b^*_{2XF'}$, $b^*_{3XF'}$, $b^*_{4XF'}$, $b^*_{5XF'}$, and $b^*_{6XF'}$, which appear as an alternating pattern of fragments differing by 161–100–161–100 Da. These differences correspond to the masses of *D*-α-hydroxyisovaleric

Table 2
Product-ion spectrum of protonated beauvericin produced by ESI [Amino-acid nomenclature: J = X (α-hydroxyisovaleryl), Z = F′ (*N*-MePhe)]

b ion series							
Protonation at oxygen (*XF′*)					Protonation at nitrogen (*F′X*)		
	b_n	a_n	$b_n - H_2O$	$a_n - H_2O$		b_n	a_n
2	262	234	244	214	2	262	234
3	362	334	344	314	3	423	395
4	523	495	505	477	4	523	495
5	623	595	605	577	5	684	656
$[M + H]^+$	784	756	766	738	$[M + H]^+$	784	756
c ion series							
Protonation at oxygen (*XF′*)					Protonation at nitrogen (*F′X*)		
	c_n	$c_n - H_2O$				c_n	$c_n - NH_3$
2	280	262			2	280	263
3	441	423			3	380	363
4	541	523			4	541	524
5	702	684			5	654	637

acid and *N*-methyl alanine residues, respectively. Second, sodium-ion attachment affords a high degree of selectivity. This is demonstrated by Fig. 1(A), which shows that the $[M + H]^+$ ions fragment to abundant c_n and b_n ions; the c_n ions are more abundant than the b_n ions. In contrast, the $[M + Na]^+$ produces nearly exclusively a set of b_n^* ions, eliminating any complications introduced by the superposition of the c_n ions upon the pattern of b_n ions. Furthermore, Fig. 1(A) and Table 2 show that each of the b_n ions from the $[M + H]^+$ probably fragments by loss of carbon monoxide. On the contrary, the b_n^* ions from the $[M + Na]^+$ ions do not lose CO. There are also no ions produced by water loss from the $[M + Na]^+$ and no detectable fragment ions arising from ring opening of the amide bonds; instead ring opening occurs exclusively at ester bonds, as illustrated in Scheme 2. Another advantage is that the $[M + Na]^+$ is formed readily, leading to high signal-to-noise ratios in the CAD spectrum.

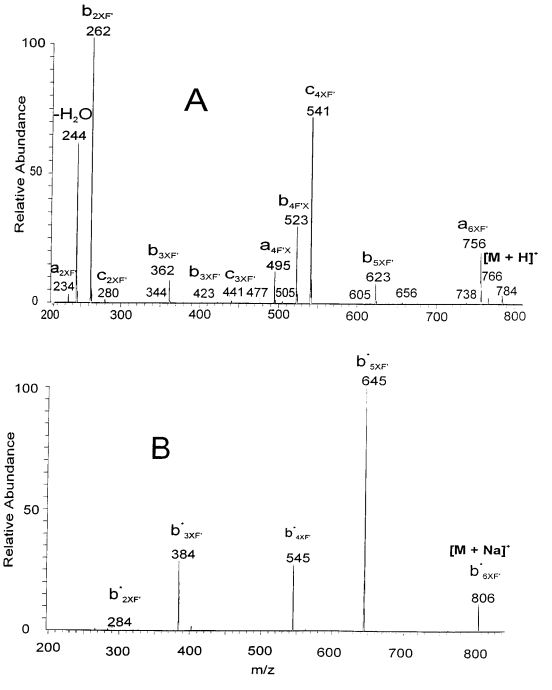
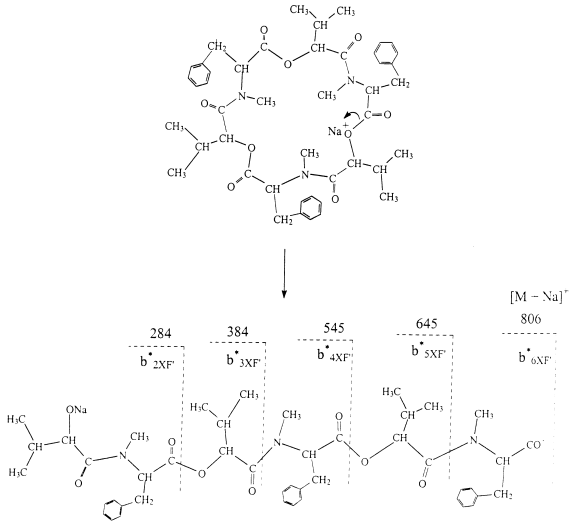


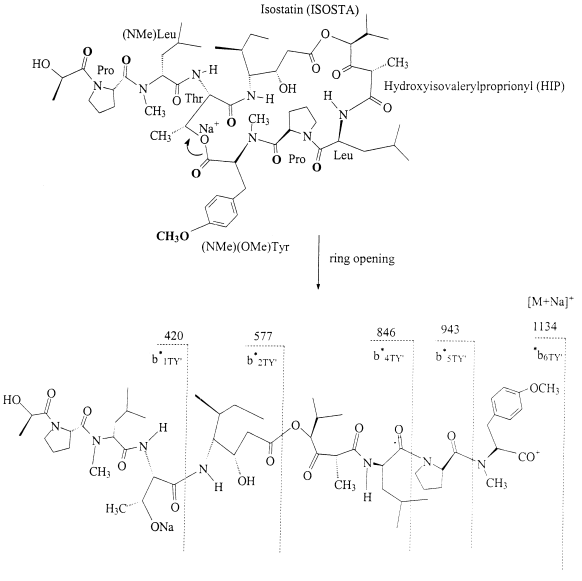
Fig. 1. Product-ion spectra of beauvericin as an $[M + H]^+$ (A) and as an $[M + Na]^+$ (B), generated by electrospray ionization. Amino-acid codes for nomenclature: J = X (α-hydroxyisovaleryl), Z = F′ (*N*-MePhe).

3.2. Didemnin B

Because all didemnins contain the same macrocyclic core structure and differ only in the linear peptide



Scheme 2.



Scheme 3.

side chain, the analytical strategy presented here applies to all didemnins. The CAD spectrum [Fig. 2(A)] of protonated didemnin B (Scheme 3), formed by ESI, was obtained with the ion-trap mass spectrometer. Collisional activation (CA) cannot break the backbone ring. Instead, ejection of the linear peptide moiety as a neutral of mass 296 occurs after intramolecular proton transfer to the threonine amide nitrogen. The side-chain fragment may also exist as an ion of m/z 297, but it was not visible in the spectrum because the mass range of the ion trap is limited at low m/z. Therefore, a tandem magnetic sector instrument, which offers wider dynamic range for mass and intensity, was used to record the CAD spectrum [Fig. 2(D)] of didemnin B $[M + H]^+$ ions that were produced by FAB. Even under the conditions of high-energy CA, the cyclic backbone cannot be broken. An ion of m/z 297, which is the linear peptide side chain, is now seen to be most abundant. Stable backbone cyclic-peptide structures were also observed by Fukai and co-workers [28] in their investigations of cyclic-peptide antibiotics. Similar observations were made by Gross and co-workers [29] on macrolide antibiotics, which fragment as $[M + H]^+$ to release the side chains as ions rather than to undergo ring opening.

In contrast, the low-energy CAD spectrum of ESI-produced sodiated didemnin B [Fig. 2(B)] shows that a selective scission of the depsipeptide ring occurs. The most abundant ion at m/z 943 arises by the loss of the (*N*-Me)(OMe)Tyr residue as initiated by a specific sodium-ion interaction at the threonine ester bond. Although didemnin B has two ester bonds in the backbone, the sodium ion either nearly exclusively binds to the ester group at threonine or there is no detectable fragmentation associated with binding at hydroxyisovalerylpropionyl (HIP). This is surprising because this molecule has numerous other accessible oxygen binding sites, including those of the linear peptide moiety. For comparison, the high-energy CAD spectrum of the $[M + Na]^+$ generated by FAB is shown [Fig. 2(E)]. The specific sodium-ion interaction and the fragmentation chemistry are essentially identical, irrespective of the methods of ionization and activation (high or low energy). Thus, the interaction of the sodium ion with cyclodepsipeptide ester bonds must be strong and highly selective. Support for the binding of sodium at the threonine-ester bond may be found in an x-ray crystal structure. Unfortunately, no x-ray structural study of a sodium complex of didemnin B has been published. The amino-acid sequence is furnished by carrying out another stage of CAD (MS^3) on the m/z 943 ion in the ion trap. The results [Fig. 2(C)] are rationalized in

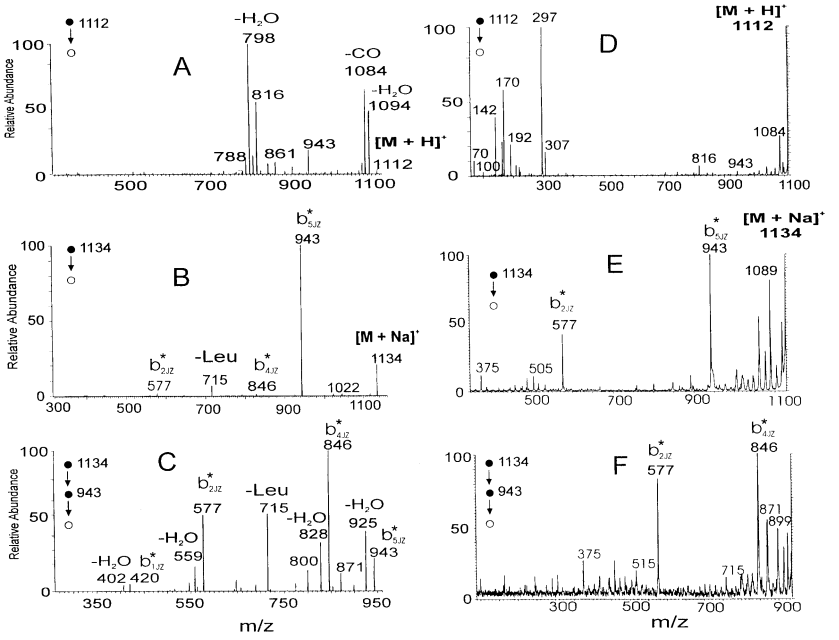


Fig. 2. Product-ion CAD spectra of didemnin B: (A) $[M + H]^+$, (B) $[M + Na]^+$, (C) ms^3 of the fragment of m/z 943, formed from the $[M + Na]^+$ by loss of the (*N*-Me)(*O*-Me)Tyr residue. Ions were generated by ESI. Panels (D), (E), (F): High-energy, product-ion spectra of didemnin B: (D) $[M + H]^+$, (E) $[M + Na]^+$, (F), product-ion spectrum of the ion at m/z 943 formed in the ion source upon FAB to give the $[M + Na]^+$. Amino-acid nomenclature: J = T (threonine) and Z = Y′[(*N*-Me)(*O*-Me)Tyr].

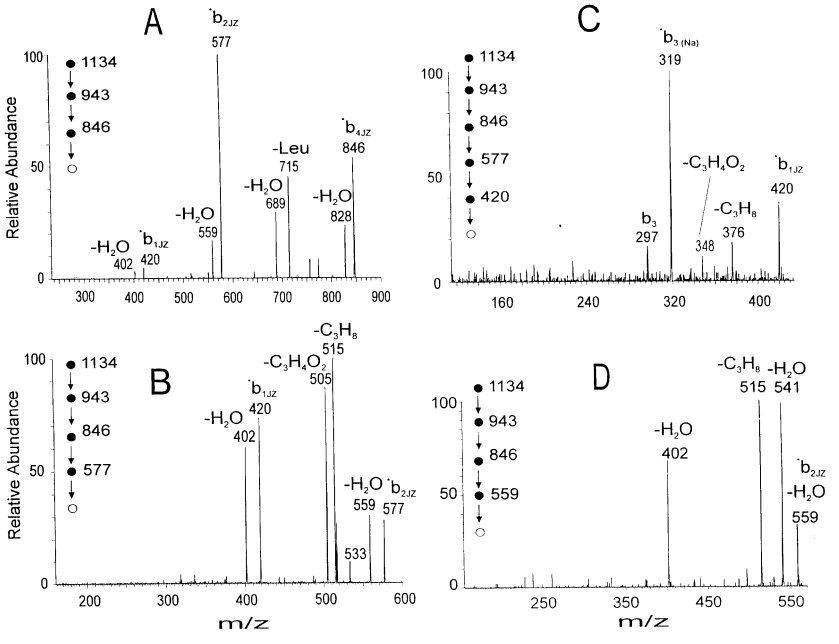
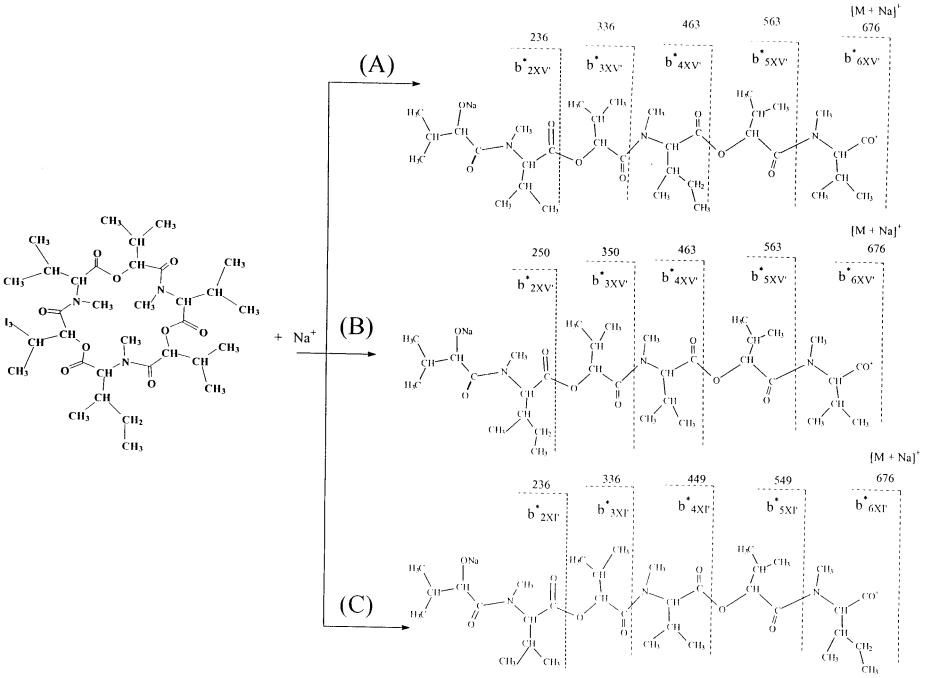


Fig. 3. Higher order MS/MS experiments: (A) MS^4 of the m/z 846 ion show that the Leu residue and HIP are lost together to form the m/z 577 ion. (B) The m/z 577 ion loses ISOSTA to form the m/z 420 ion. (C) MS^5 of the m/z 559 ion, which arises by water loss from the m/z 577 ion and then loses ISOSTA to form the m/z 402 ion. (D) MS^6 of the m/z 420, which loses the Thr residue to afford the m/z 319 ion. Amino-acid nomenclature: J = T (threonine) and Z = Y′[(*N*-Me)(*O*-Me)Tyr].



Scheme 4.

Scheme 3. The ester linkage between Leu and HIP could not be broken, even under high-energy CA [Fig. 2(F)], where the *m*/*z* 943 ion was generated directly in the FAB source.

Multiple stages of CAD experiments were executed on several of the ions observed in the spectrum in Fig. 2(C) to ascertain their genealogies (Fig. 3). Collisional activation of the $b^*_{4TY'}$ ion at *m*/*z* 846 in an MS^4 experiment results in the simultaneous ejection of the Leu and HIP residues to form the $b^*_{2TY'}$ ion at *m*/*z* 577, which loses the isostatin (ISOSTA) residue to form the $b^*_{1TY'}$ at *m*/*z* 420. These reaction sequences are confirmed by the MS^5 spectrum in Fig. 3(B). Execution of MS^6 experiment on the $b^*_{1TY'}$ ion of *m*/*z* 420 [Fig. 3(C)] causes four reaction channels to open. First, an intramolecular protonation of the proline nitrogen with the hydroxyl proton of the α-hydroxypropionyl residue is proposed to lead to cleavage of the α-hydroxypropionyl-Pro amide bond to give ejection of the α-hydroxypropionyl as a neutral species and the shortened peptide as an ion of *m*/*z* 348. Second, the heterolytic scission of the *N*-MeLeu–Thr amide bond furnishes the linear pep-

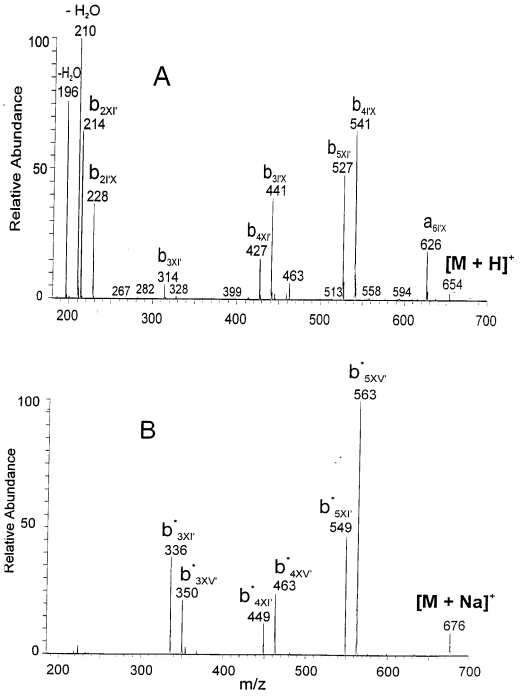


Fig. 4. Low-energy CAD spectra of enniatin B1: (A) $[M + H]^+$, (B) $[M + Na]^+$ ions produced by ESI. Amino-acid nomenclature: J = X (α-hydroxyisovaleryl), Z = V′ (*N*-MethylVal), Z = I′ (*N*-methylisoleucine).

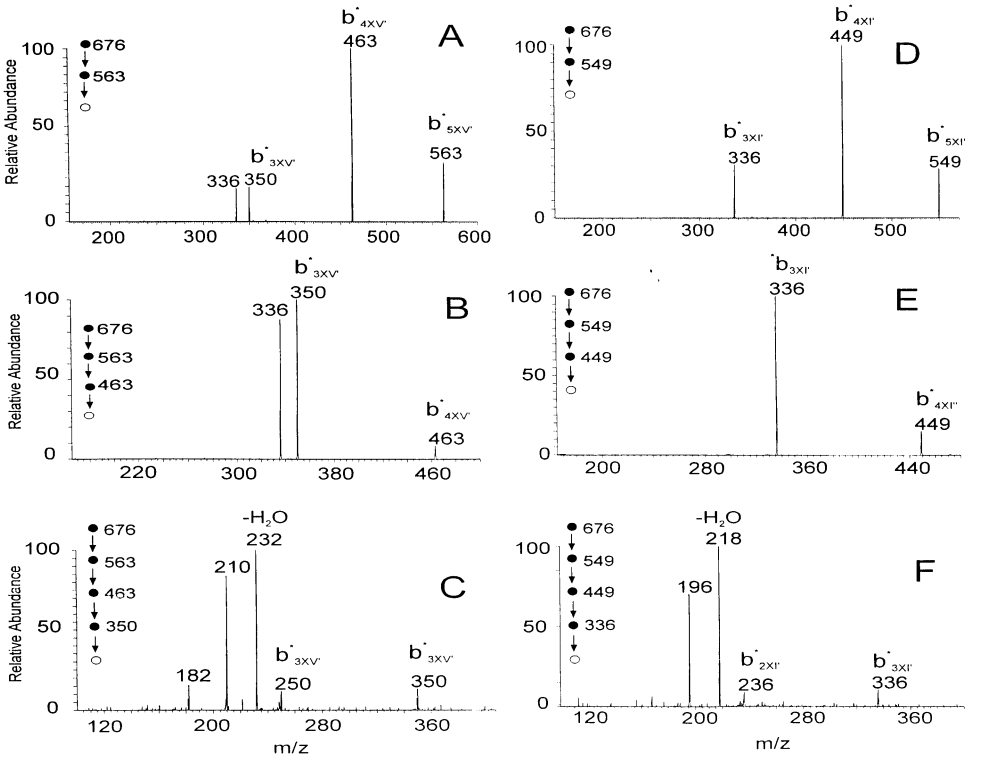


Fig. 5. Higher order MS/MS experiments of sodiated enniatin B1: (A) MS^3 of the m/z 563 ion. Loss of α-hydroxyisovaleryl residue furnishes the ion at m/z 463. (B) MS^4 of the m/z 463 ion. Loss of *N*-methylvalin affords the $b^*_{3XV'}$ ion at m/z 350. (C) MS^5 on $b^*_{3XV'}$ ion at m/z 350. (D), (E), and (F): Multistep CAD experiments showing fragmentation of the peptide when primary ring opening occurs between α-hydroxyisovaleryl residue and *N*-methylisoleucine. Amino-acid nomenclature: J = X (α-hydroxyisovaleryl), Z = V′ (*N*-methylVal), Z = I′ (*N*-methylisoleucine).

tide moiety α-hydroxypropionyl–Pro–*N*-MeLeu$^+$ at m/z 297. In this reaction, the threonine residue is lost as a neutral species. Third, transfer of Na^+ occurs from the threonine residue to the linear peptide moiety to give the m/z 319 ion and loss of a Thr residue. Fourth, the elements of C_3H_8 are lost from the *N*-MeLeu side chain.

Because the linear peptide moiety was not accessible in the product-ion spectra of the ion trap, ESI-source CA was used to generate it. The product from the ESI-source reaction was then selected as the precursor ion for subsequent CA experiments. Its product-ion mass spectrum (not shown) was essentially dominated by the loss of the *N*-MeLeu residue to give an m/z 170 ion. Losses of carbon monoxide from the b_3 and b_2 ions also occur.

3.3. Enniatin B1

The product-ion spectrum of the $[M + H]^+$ of enniatin B1 (Scheme 4) is a superposition spectrum consisting of fragments from all ring-opening possibilities [Fig. 4(A)]. As for the CAD spectrum of beauvericin [Fig. 1(A)], it is difficult to derive from it the amino-acid sequence. In contrast, the spectrum of the sodiated molecule [Fig. 4(B)] furnishes simpler sequence information. Because enniatin B1 consists of three residues of α-hydroxyisovaleric acid, two residues of *N*-MeVal, and one of *N*-MeIle, the interaction of a sodium ion with three ester bonds in the backbone leads to three ring-opened acylium ions. As a result, the CAD spectrum of the sodiated enniatin B1 [Fig. 4(B)] is also a superposition spectrum,

consisting of three patterns of overlapping fragments. All the b^* ions generated by the ring-opened acylium ions are illustrated in Scheme 4. These were isolated and sequenced separately by using several stages of CA (Fig. 5). The MS^3 experiment of the ion of m/z 563 [Fig. 5(A)] shows that it is a mixture of structures even though it is formed by the loss of the *N*-MeVal residue from the $[M + Na]^+$. The mixture components are α-hydroxyisovaleryl(Na) – *N*-MeVal-α-hydroxyisovaleryl – *N*-MeIle–α-hydroxyisovaleryl$^+$ and α-hydroxyisovaleryl (Na)–*N*-MeIle–α-hydroxyisovaleryl–*N*-MeVal–α-hydroxyisovaleryl$^+$.

4. Conclusion

The sodium ion binds to the lactone of cyclodepsipeptides with high specificity. Even for cyclodepsipeptides with more accessible oxygenated functional groups in their chains or with a linear-peptide moiety, the binding site of the sodium ion that leads to structurally informative reactions is always the ester oxygen of the cyclic backbone. This interaction opens the ring, giving a linear acylium ion that undergoes selective fragmentations to furnish the amino-acid sequence. This specific interaction applies to cyclodepsipeptides of various types, owing to the oxyphilicity of the sodium ion.

This approach is a simple, completely instrumental determination of cyclodepsipeptides, obviating the need for chemical derivatization of the analyte.

Acknowledgements

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